Appendix A
Example - ADD

METHOD:

Two individuals were referred for Career Evaluations by their Mother because they lacked ambition and success in work. They were a 27 year old female and her 25 year old brother. They shared the same biological parents, both professionals, and shared similar behavior characteristics of:

- Completing Junior College in 4+ years.
- No record of full time employment for 4 months or longer.
- Limited friendships.
- No specific career plans.
- Enthusiastic beginnings but poor or incomplete endings.
- Underachievement in relation to ability.

Both were administered a battery of tests which measured neuropsychological functioning and personality variables. The similarities continued with both scoring in the superior range on a non-verbal abstract thinking intelligence test; average on the Vocabulary subtest of the Wechsler Adult Intelligence Scale- Revised; average in fine motor coordination and organization.

Both scored low on achievement motivation, affiliation and the ability to ask for assistance when they had no solution to a problem. They were high on aggression and needed control.

On referral for neurological evaluation, mild physical and significant objective testing abnormalities were found. Both patients exhibited very mild balance difficulties only identified on careful neurological testing. The patients had a mild tendency to sway when standing at attention with their eyes closed (abnormal Rhomberg testing). Both, further, had difficulty performing a Tandem Gait with complete ease. The physical exam was otherwise normal. An EEG and computerized EEG were performed and were abnormal. These tests showed a frontal and temporal spatially distributed alpha rhythm on an average referential montage. Transcranial Doppler ultrasound showed middle cerebral artery velocities of greater than 0.8 meters/second bilaterally in the female, and 0.73 meters/second in the right MCA of the male, with a normal 0.26 meters/second in the left MCA. Interestingly, on a separate day, the male was retested and found to have elevated MCA flow velocities of 0.86 meters/second on the right, and 0.92 meters/second on the left.

Example ADD:
TREATMENT:

Both individuals were treated with vasodilating medications for 10 months and received psychotherapy and vocational counseling. Relaxation and hypnotherapy were also used to

develop visualization skills for both recall of successful social and work experiences and to visualize successful outcomes of activities to do.

In serial testing, the male underwent TCD's on three separate occasions on the same day. After repetitive applications of Nitroglycerin, the patient was re-examined and underwent self-assessment, and had repeat Transcranial Dopplers performed. As the right MCA mean flow velocity decreased from 0.86 meters/second to 0.79 meters/second, to 0.72 meters/second, and the left MCA mean flow velocity decreased from a baseline of 0.92 meters/second, to 0.84 meters/second, to 0.79 meters/second, the patient's exam progressively normalized with eventual development of completely normal balance testing. The patient also identified significant improvement in concentration. By the end of the day, he identified that he could read, understand and retain news articles and magazine articles. He could also follow a television show throughout. He could do neither at the beginning of the day. Observers also felt his comprehension had significantly changed.

On the basis of the objective disorders of flow and the patient's reported and observed improvement during the trial episode of administering medications to decrease the observed vasospasm, we started the brother on vasodilators. After the patient had been on medication for approximately 3 months, the sister's observations of significant improvement in her brother's functioning resulted in her self-referring for evaluation and treatment. We initially used Nitroglycerin and later added a variety of Angiotensin Converting Enzyme inhibitors, Calcium Channel blockers, and Clonidine until the regimen that the patient best tolerated was found. This regimen was made up of a low dose Calcium Channel Blocker, and an ACE inhibitor along with low dose Nitroglycerine and a Clonidine patch.

Over the next 6 months, both sibling's neurological exams normalized. The Transcranial Doppler results showed marginal improvement from office visit to office visit. However, the patients have identified significant functional improvement which wears off in direct relationship to the vascular pharmacokinetics of the specific medication used.

Example ADD:
RESULTS:

Both the male and female subjects experienced social, emotional, physical and intellectual gains through these treatments. Their Verbal IQ scores increased from scores of 110 and 119 to 143 and 146 respectively. On the Bender Gestalt Test they eliminated all errors and their drawings were better organized with improved fine-motor coordination. Both have been planning a continuation of their college education with specific goals in mind. The young man had played tennis in high school and has maintained playing recreationally. He had noted specific improvements in anticipating moves of his opponents and had improved his

game significantly. This was also noted by his opponents and fellow tennis teacher.

Their personalities changed significantly. The female became less fearful and argumentative and was self assured. The male as stated "I can relate to friends and I am not the last to get the joke. I am less the point of jokes and teasing." These were significant personality and social changes for these individuals.

Example ADD:
DISCUSSION OF POSSIBLE THEORY:

This study utilized siblings who had been considered OK in life, but themselves were frustrated and had self thoughts of failure. Based on Career Neuropsychological testing, they were found to be Adult-ADD. After 10 months of treatment with vasodilating medications and psychotherapy, they have improved their cognitive, social and emotional functioning. Their gains have been significant and have stabilized. These have remained consistent for over 11 months and indicate a permanent solution.

From a neurological viewpoint, serial monitoring identified close relationship between functional abilities and a degree of vasospasm or constriction of the arteries. These patients' long term TCD's do not reflect major improvements in the resolution of the degree of spasm. The lack of complete resolution of the vasospasm probably relates to, in these two specific patients, their inability to tolerate even moderate levels of vasodilators without developing symptomatic hypotension. These two patients share in common with all Applicant's patients referred for idiopathic Attention Deficit Disorder that we can seldom completely resolve the vasospasm identified on ultrasound, but that any improvement in the arterial constriction parallels functional improvement. Patients with secondary Attention Deficit Disorder-like syndromes, such as are seen after trauma, closed head injury, neck injury, Reflex Sympathetic Dystrophy, cerebrovascular accident, silicon implant disease and other toxic vasculopathies, and so on, generally have profound vascular relaxation with the commonly used vasodilators after approximately 6-10 months of treatment. Nonetheless, our therapy in these two patients has probably been successful by causing vasodilation of the small arterioles and other blood vessels in the brain. Such vasodilation would decrease the ischemia of the brain tissue and improve performance. On a day when serial testing was performed when repetitive vasodilation medication doses were used to decrease the vasospasm, the patient showed significant improvement. This argues that improved control of the vasospasm may be expected to cause further functional improvement. Equally, it is strongly recommended that psychological counseling and biofeedback be utilized in the long term treatment of these patients, as such treatment, by decreasing autonomic nervous tone, also enhances vasodilation.

Example ADD:
Literature

Learning disabilities (LD) and attention deficit hyperactivity disorder (ADD) represent almost 25% of school age learning - conduct problems. Despite their prevalence, much confusion exists over the differentiation between LD and ADD. This confusion emanates from the fact that some individuals suffer from both disorders and school systems tend to group both disorders in the same classroom or diagnostic category. The major confusion results from the failure to appreciate the considerable progress that has been made in recent years in defining and classifying each of these common neurocognitive and neurobehavioral problems (Shaywitz, et.al., 1995, p.s50).

Hallowell & Ratey, 1994 have found that a large number of adult patients viewed as depressed, anxious, obsessivecompulsive, personality disordered, dissociative or prone to substance abuse were ADD. Until recently mental health professionals have not paid much attention to this disorder in adults, despite the fact that attentional disorders have major ramifications for intellectual, cognitive and emotional experience. Miller, in a Wall Street Journal article in 1993, identified the following as symptoms of ADD in adults:

- A short attention span, especially for low-interest activities.
- Enthusiastic beginnings but poor endings.
- Low frustration tolerance.
- Difficulty listening.
- Argumentative.
- Frequent job changes.
- Underachievement in relation to ability.
- Frequent and unpredictable mood swings.
- Avoids group activities; a loner.
- Spends excessive time at work because of inefficiency.

Example ADD:
BIBLIOGRAPHY

Hallowell, Edward M. and Ratey, John J. Answers to Distraction, Pantheon Books, New York, 1994, p. 207-211.

Shaywitz, Bennett A., Fletcher, Jack M., and Shaywitz, Sally E., "Defining and Classifying Learning Disabilities and Attention - Deficit/Hyperactivity Disorder.", Journal of Child Neurology, Vol. 10 Supplement Number 1, Jan., 1995.

CONCUSSION OR POST-CONCUSSION SYNDROME

PROFESSIONAL ABSTRACT

This article represents the first discussion that concussion and post-concussion symptoms as well as progressive deterioration after an accident may be vascularly mediated.

Progressive deterioration of patients, as well as patients complaining of concussion or post-concussion syndrome or closed head injury, should include vascular ultrasound screening of the brain.

This paper represents a complete evaluation of twenty-two patients referred for evaluation of concussion and post-concussion syndrome. All patients on referral from their primary treating physician or psychologist also carried the diagnosis of concussion. All patients complained of progressive deterioration starting some time after an accident.

Six of 22 patients had a loss of consciousness, 7 of 22 patients had altered mental status at the time of the accident which cleared completely, and 9 of 22 patients had no concussion or mental symptoms; only spinal symptoms (2 of these 9 did have a headache). It is assumed that one third of the patients did not have a brain injury at the time of impact. An additional one third had complete resolution of all symptoms after the trauma. However, by the time of presentation, all had an abnormal neurological exam and symptoms of concussion, closed head injury and post-concussion syndrome.

All patients were found to have vascular flow abnormalities by the Transcranial Doppler (TCD) showing evidence of abnormal constriction of the arteries intracranially. Other imaging modalities of these patients included CT and/or MRI scan in all patients, EEG and computerized EEG in all patients; SPECT scan and neuropsychological testing were additionally added in many patients. The comparison of these various imaging and diagnostic modalities is made.

Example - CONCUSSION OR POST-CONCUSSION SYNDROME

Comparative Analysis and Evaluation

Twenty-four patients having been computer coded as concussion syndrome were chosen at random per data from the office computer; the patients were seen in this office between February 23, 1995 through January 1996. Two of the patients were miscoded and were dropped from this study. All patients were referred by their primary physician or psychologist with the diagnosis of concussion. Injuries of twenty patients were sustained by motor vehicle accidents and two patients' injuries were a result of falling. Each patient was given a neurological examination by a board certified neurologist, Transcranial Dopplers, standard and quantitative EEGs, and most were given either/or MRIs or CT scans of the brain, neuropsychological testing, and three patients had SPECT Scans of the brain .

Example - CONCUSSION OR POST-CONCUSSION SYNDROME

CLINICAL PRESENTING SYMPTOMS:

Loss of consciousness varied with patients having very brief black-outs of seconds to twenty-five minutes. Six patients had a loss of consciousness at the time of the accident with four patients unconscious for brief seconds, one patient for five minutes and one patient about twenty four hours. (Ref.Table IA. Period of Total Unconsciousness at Scene of Accident with Other Related Symptoms)

There were seven patients that denied loss of consciousness but had less severe altered mental status such as amnesia, mental confusion, dazed, dizziness, vertiginous and/or ataxia. (Ref.Table IB . Altered Mental Status With No Unconsciousness and Related Symptoms)

A third class of patients consisted of nine patients who had no altered mental status but experienced a combination of a variety of symptoms such as neck and back pain (two of them also had a headache). One patient had no symptoms at all at the time of the accident but developed severe back pain later at night following the accident. (Ref. Table IC. Physical Symptoms With No Altered Mental Status.)

Table IA. Period of Unconsciousness at Scene of Accident and Other Related Symptoms

# of Patients	Period of Total Unconsciousness & Related Symptoms
4	Brief loss of consciousness with neck and back pain of seconds to less than 5 minutes
1	Loss of consciousness for 5 minutes. dazed. confused with neck and back pain
1	Loss of consciousness for about 24 hours & awoke with neck and back pain

Table IB. Altered Mental Status With Related Symptoms But No Total Unconsciousness

3	Immediate severe headaches. confusion. neck and back pain
1	Neck and back pain. vertiginous and nausea
3	Amnesic for accident. confusion. back and neck pain

Table IC: Physical Symptoms With No Alter Mental Status

2	TMJ and neck pain
1	Neck pain only
3	Neck and back pain
2	Headaches and severe neck pain
1	No symptoms at all at time of accident but later that night developed back pain.

Example - CONCUSSION OR POST-CONCUSSION SYNDROME

ADDITIONAL PHYSICAL SYMPTOMS:

TEMPOROMANDIBULAR JOINT INJURY

An associated finding in this study was TMJ and facial pain. Of the twenty- two patients studied fifteen patients had pain in the temporal mandibular joints with ten of the patients diagnosed with having TMJ and five patients with mild symptoms of popping of TMJ was considered to be clinically insignificant. Onset of symptoms varied from immediate discomfort to four months post the accident. Some of patients that were later diagnosed as having TMJ related that in the beginning, they had so much head and facial pain that they were not able to determine where the pain was coming from until they have had a

chance for some of the injuries to heal. (Ref. Table 1D. Time of Onset of TMJ Symptoms Following Accident)

Table 1D. Time of Onset of TMJ Symptoms Following Accident

5 patients don't know when pain was localized to TMJ
2 patients had immediate pain in TMJ
1 patient had pain about two hours later
3 patients had pain not immediately but within twenty-four hours of trauma

1 patient with previous treated TMJ became worse within twenty-four hours following new injury
3 patients' pain was localized to TMJ 2 months post accident

Example - CONCUSSION OR POST-CONCUSSION SYNDROME

THORACIC OUTLET SYNDROME:

A common associated complaint was symptoms of upper extremity intermittent paresthesias consistent with Thoracic Outlet Syndrome. Only rarely debilitating, and not complained of by the patient unless checked for during a Review of Systems of 22 patients. (Ref. Table 1E.).

Table 1E.

19 had Thoracic Outlet Syndrome.
3 had no symptoms of Thoracic Outlet Syndrome.

INTERVAL BETWEEN DATE OF INJURY AND PRESENTATION:

Time lapse between the date of injury and the patient's initial office visit varied from two weeks post accident to years.
(Ref. Table II, Time Lapse from Date of Accident & Initial Office Visit)

Table II. Time Lapse from Date of Accident & Initial Office Visit

# of Patients	Lapse time injury and initial office visit
1	11 days post accident
3	1 month
2	2 months
4	3 months
1	4 months
1	5 months
3	6 months
1	7 months
1	8 months
1	14 months
1	16 months
2	3 years
1	25 years

PREVIOUS HISTORY OF HEAD INJURY:

An interesting finding during this survey was that 50% of the patients have had at least one previous accident.(Ref. Table III. Previous History of Head injury. Two of these patients had loss of consciousness, one for less than 24 hours and the other patient, with a Glasgow Score of 4, was unconscious for three months. (Ref. Table III, Previous History of Head Injury)

Table III. Previous History of Head Injury

13 patients had never had a previous accident
4 have had 1 previous accident
2 have had 2 previous accidents
3 have had 3 previous accidents

Example - CONCUSSION OR POST-CONCUSSION SYNDROME

CLINICAL PRESENTING SYMPTOMS SUMMARY

All patients developed delayed and progressive symptoms which consisted of as neck and shoulder spasms, migraine headaches, memory and concentration problems, easy distractibility in an attention deficit-like disorder, and most complained of intermittent upper and/or lower extremity paresthesias due to
associated spinal injuries. Most patients complained of intermittent balance problems of varying, usually mild severity, tinnitus and/or visual blurring were also frequent complaints.

Example - CONCUSSION OR POST-CONCUSSION SYNDROME

TESTING RESULTS:

The patients were evaluated using multi-modality neuro-diagnostic and imaging techniques. vaso A discussion of MRI, SPECT scan results, neuropsychological testing, Transcranial Doppler, EEG and QEEG follows. All modalities proved to be of value.

EEG AND QEEG RESULTS:

With respect to EEG's, correlation of the abnormalities seen in the standard and quantitative EEGs are very close in some cases, but in other cases abnormalities are seen in the standard EEG that are not seen in the qualitative EEGs and vice versa. The most common feature observed in the standard EEG being an alpha-like rhythm occurring bilaterally in the frontal and temporal areas that was disassociated from the posterior alpha band seen only on an average referential montage. The quantitative EEG's most common finding was an underlying-slowing in the theta and/or delta
frequency range located bilaterally in the frontal and temporal areas and at times appearing in the posterior head regions. Epileptogenic spike discharges obvious in both standard and quantitative but not in the averaged EEG. However, the QEEG aided in localization of the discharges with further analysis. (Ref. Table IV, Comparison of Findings of Standard and Qualitative EEGs)

Table IV. Comparison of Findings of Standard and Quantitative EEGs:

A. Summation of Standard and Quantitative EEG Findings:

18 Patients had abnormal standard and quantitative EEGs
4 Patients had normal standard and quantitative EEGs
2 Patients had epileptogenic spike discharges obvious in both standard and quantitative EEGs but not in the average EEG.

EXAMPLE - PSYCHOSIS CAUSED BY CEREBRAL ISCHEMIA

PROFESSIONAL ABSTRACT:
A patient with a schizophrenic reaction after a long history of migraines is presented. The patient was hospitalized for an acute psychotic break. Due to difficulty with regulating the thought disorder, the hospitalization was extended to 3 weeks. On discharge, the patient self-discontinued her medications with a return of headaches and thought disorders. Evaluation of her including EEG and vascular evaluation of the brain showed abnormalities. The patient was placed on medication to treat the vascular constrictive disorder and the patient's thought processes returned to normal and the patient became headache free.

CASE STUDY

The patient presented with a long history of migraine headaches which had progressed over the year prior to development of her schizophrenic break. The headaches would become daily. The patient noted at times, due to the headaches, she would have intermittent degrees of confusion, disorientation or memory disturbances. She had no history of seizures. Two months prior to presentation she became increasingly distressed about personal family issues with aggravation of the headaches. She treated herself with over-the-counter medications and then became concerned that her husband might be leaving her. She went down to meet him at his place at work, but became confused about how to enter the building, and decided he was probably trying to leave the state. She stole a truck, drove along the road she thought would lead to him. She was followed by police who identified her as having disorientated thought processes. She was hospitalized for psychological evaluation, was found to have a reactive psychosis and schizophreniform disorder.

The patient continued to have hallucinations and delusions, was placed on Haldol (Haloperidol) from which she did not respond. Headache was not a significant complaint in the hospital. She was eventually placed on a combination of Navanne (Thiothixene) and Ativan (Lorazepam). She improved significantly. Blood work including thyroid studies were normal. The patient was released and continued to have severe headaches, concentration problems and memory problems. She felt these problems were aggravated by activity. Her neurological examination was normal. A CT scan of the brain was obtained which was normal. An EEG and a QEEG showed intermittent left temporal spike discharges, as well as bifrontal temporal slowing activity in the 5 mv range in the delta and theta patterns. A frontal alpha frequency band was also identified on an average referential montage as well as the computerized EEG. Transcranial Doppler Artery showed evidence of mean flow velocities in the MCAs bilaterally of .65 to .75 meters per second, and the basilar artery of .7 meters per second.

The patient was placed on Inderal (Propranolol) as well as Depakote (Sodium Valproate) without change in her EEG and continued flow abnormalities on Transcranial Doppler Artery.

The patient was then placed on Nitroglycerin with complete resolution of her daily headaches and improvement in her middle cerebral artery flows to the normal range.

While taking Nitroglycerin medication, the TCDs continued to improve with MCAs approaching .37 meters per second to .5 meters per second. The patient's headaches completely resolved as did memory disturbances, concentration problems and emotional lability.

DISCUSSION

The patient has a long history of migraine and develolped migraine and/or stress-induced schizophrenic reaction. She had poor response to Haldol (Haloperidol), but good response to Navane (Thiothixene). On presentation to the neurologist's office, the patient was off Navanne and evidence of vasospasm and evidence consistent with cerebral ischemia as well as the spike discharge was identified on EEG. The patient did not respond to standard antimigraine medication or seizure medication. The patient responded promptly to low-dose Nitroglycerin for control and management for migraines with no recurrent episodes of thought process disorders, memory disorders or disorientation when taking medication.

This suggests that some patients with vasospasm and vasoconstriction with secondary ischemia of the brain may develop neurocognitive changes including psychosis. Applicant has had several other patients with diagnoses of chronic depression or of steroid induced psychosis, in these cases headache was not a complaint, who had similar vasospasm identified on Transcranial Doppler and similar EEG changes as this patient. They also responded with clearing of their psychiatric disorders with vasodilators. It is thus our recommendation that, in the evaluation of the psychotic or psychiatric patient, evaluation for vasospasm and cerebral ischemia should be performed and treatment instituted empirically to reverse any abnormalities found, as the psychiatric disturbance may have a vascular component.

MIGRAINE FORUM (WHIP-LASH/BREAST IMPLANTS/MIGRAINE)

Applicant has a baseline practice consisting of mainly post-traumatic, closed-head injuries and post-traumatic migraine disorders of which many have attention deficit disorders, (ADD). However, several years ago Applicant had a large number of patients who presented with ADD of which the origin of their problems was associated with silicon breast implants (silicon toxicity). What became evident in evaluating of these patients was that the neuropsychological tests, computerized EEG and Transcranial Artery Doppler results were essentially identical. Another common characteristic in these patients was the waxing and waning nature of at least some of their complaints. Those patients with Attention Deficit Disorder both post-traumatic and in particularly those patients with silicon breast implant disease with MS-like syndrome would have normal neurological examination one day and on another day the exam would be normal. This finding substantiated the patients' complaints of waxing and waning of symptoms and

seemed to be related to the degree of physiological or psychological stress the patient experienced when being interviewed or tested.
The degree of abnormality of neurological exams would extend to the point of normal or abnormal Romberg and Tandem Gaits, reflex examinations and Babinski examinations in the same patient. Evoked potential test results varied from normal to abnormal on different
days and the testing was performed by the same examiners.

In this same time frame, a series of new medications were developed to treat migraine headaches. As headache was a major complaint of many of Applicant's patients, we tried these medications out including Imitrex (Sumatriptan), IM Toradol (Ketoralac) and other medications under direct monitoring. As Applicant's patients tend to be intractable, it was not expected that any of these medications would have dramatic results. Rather, it was expected that one or another set of medications might help point the way into using specific classes of medications or approaches. Accordingly, each of these patients, equivalent of a large number of patients, were monitored continuously across the day. The patients would come in and be hooked up with EEG's or Brain Stem Auditory Evoked Responses, or VEP's, or Transcranial Dopplers, and across the day would have many of the different short-acting medications tried on them to see which would work and which monitoring tool would be most effective in identifying the improvement.
With respect to the different monitoring tools, some were more helpful than others. It was found that the EEG was not very sensitive. The Brain Stem Auditory Evoked Response and other evoked potential tests were very insensitive tools for monitoring, because of the length of time required to perform the test after short-acting medications were given in IM or sublingual or nasal spray administration route. The Transcranial Doppler consistently appeared to give the best indication as to which medications would work. If an ultrasound showed improvement, the patient invariably also reported improvement in their clinical symptoms. These symptoms included not only headache, but also sensations of confusion, balance disorder, abnormal Romberg or Tandem Gait or other neurological abnormalities. If the medications showed evidence of increasing vasoconstriction on the doppler, the patients who had a headache, frequently reported improvement in the headache, but a worsening of their confusional state or a worsening of other neurological symptoms. Those patients were identified as having improvement on ultrasound with doppler also showed resolution of their headache, but did not show the deterioration in their neurological effects. This was completely unexpected. The general approach towards migraine and headache has always been that the headache represents a vasodilation and frequently a hyperperfusion state. The aura, of course, represents a vasoconstrictive phase. What our results seemed to suggest was that the doppler, which looks at essentially the area of blood vessels around the base of the brain, was showing vasoconstriction. Vasoconstrictive medicines would relieve the headache presumably through a similar mechanism, as a vasoconstrictive medication probably relieved coronary artery disease. It would relieve it by decreasing the vasodilation that occurs downstream from the area we are able to directly insonate.
Unfortunately, if cerebral artery disease is anything like coronary artery disease, that downstream dilation represents an attempt by the body to compensate and maintain perfusion to thus becoming ischemic.
In Applicant's patient population all medications which resulted in vasoconstriction, relieved the headache, but caused neurological deterioration. As the medication wore off, as documented by the patient's clinical symptoms, sonography data, the patient's neurological abnormalities improved. Similarly, those medicines which resulted in direct

vasodilation such as Hydralazine (Apresoline), Nitroglycerin and other medications all resulted in improvement in the patient's headache. but also resulted in improvement of any other neurological abnormalities including balance disorders, gait disorders, hemiparesis, abnormal Babinski's and abnormal reflexes.

OBSERVATIONS NOTED CONCERNING TRANSCRANIAL DOPPLERS

A special word about Transcranial Doppler needs to be made. We found that morphology of a Transcranial Doppler Artery Ultrasound is as important as mean flow velocities. In our patients, as they became more normal, and as their fixed deficits and europsychological abnormalities resolved etc., the morphology of the wave form would be similar to that of an internal carotid artery tracing. We did not find that there would be elevation of flow readings throughout diastole, as is more commonly published. It is important to identify that the original normative data obtained in 1979, used for "Normals" patients with post-traumatic migraine disorders, "psychogenic seizures", and the interictal migraine phase may not be appropriate. It is important to note that other labs which have done less extensive studies of normal versus non-normal, may have unknowingly used many patients with a history of migraines or whiplash headaches. Some have not identified the close relationship between degree of vasospasm and clinical abnormalities. This may be due to less lengthy monitoring or evaluations being carried out by those labs in comparison to our own. Equally, the trend clinical correlation is a general one. Remembering hemodynamics, it is important to note that if the blood vessel is constricted, patients do have a limited ability to compensate for the effects of that vasoconstriction by dilating distally to the constricted area.

Patients will not be abnormal clinically during the early stages of constriction of an artery. It is only once the downstream area is no longer able to dilate to a degree enough to maintain a significant pressure gradient across the vasoconstricted area that the patient will develop symptoms. It is important to continue to monitor and treat these patients until the sonographic studies return to normal and beyond. Realizing that blood vessels constrict across the day in response to sympathetic nervous system variability, internal steroid release, physiological and psychological stress, including the physiological stress of photic stimulation, driving etc., and thus to obtain an ultrasound at one moment, must be correlated with the patient's clinical symptoms and any complaints of variability across the day.

We also found that over time, chronic, untreated patient studies frequently falsely appear to normalize with a dropping of mean flow velocities. This occurs as the body develops compensating mechanisms to relieve the ischemia. Thus morphology becomes extremely important in identifying those who have ongoing vasoconstrictive disorder intracranially. The development of a pattern as time goes on is to have a blunted upstroke in the systolic portion of the ultrasound, but with an overall mean flow velocity of less than .6 meters per second. That blunting, which is also seen in disseminated vascular disease from any cause, is highly suspicious for severe vasospastic disorder. A computerized EEG or standard EEG consistent with brain dysfunction or ischemia, and/or neuropsych testing consistent with variability of cognitive injury (especially with fluctuating cognitive deficits across several hours or days of testing) with ischemia is often helpful corroborating study. These are patients who should not be treated initially with Nitroglycerin or other potent medications, but should first have other medications which are direct vasodilators instituted at low doses and slowly advanced as the patient is able to tolerate it. This institution with alternative vasodilators, tends to decrease the incidence of a potentially dangerous nitric oxide sensitivity reaction.

With respect to Nitroglycerin, what we have seen is several time courses of the effect of Nitroglycerin. The first is an acute effect which lasts between 15 and 45 minutes. The method of administration being a patch, pill or sublingual spray determines the rapidity of absorption and distribution. It seems to have a lingering effect for approximately 2 to 3 hours. Nitroglycerin then gets converted into a variety of subsidiary byproducts, all with some vasodilating properties. Each of these medications themselves can accumulate in patients to toxic doses, and can cause a reactive cerebral vasoconstriction. Thus, it is easier to maintain patients on intermittent low dose Nitroglycerin applications, then chronic applications of medication, as the clinical data and clinical response to the vasodilator challenge becomes confused. With respect to Nitric Oxide sensitivity, those patients in Applicant's clinical practice who have not been premedicated with a beta blocker, an alpha blocker or a direct vasodilator such as a calcium channel blocker or an ACE inhibitor, who are given their first dose of Nitric Oxide and developed acute erythema of the nose or face, are having a reactive vasoconstriction and distal vasodilation occurring at the same time. Those patients on Transcranial Doppler Artery Ultrasound will have acute spasm of the arteries and active constrictions and dilations may frequently be seen. Those patients may have a seizure or a stroke or a blackout spell. This problem can be immediately reversed with IM Toradol (ketoralac). Toradol in 90 to 120 mg IM doses causes acute vasodilation on ultrasound in most patients. In lower doses, the Transcranial Doppler Artery ultrasounds generally do not show significant changes, but the patient reports a symptomatic improvement. For most patients, standard doses of nitrates in any
form will aggravate the vasospasm.

IV Toradol (Ketorolac) in 30 to 60 mg doses does not cause any improvement on Transcranial Doppler Artery Ultrasound, and patients generally report a sensation of vertebrogenic syndrome with increase spaciness, confusion, worsening headache and worsening spasm. Although Applicant has not identified this directly, their clinical course is that of a development of a vasoconstricted vertebral or basilar artery syndrome. This probably relates to a carrier drug in the I.V. Toradol solution, as giving the Toradol intramuscularly (I.M.) or in the alternative oral form after oral or I.M. loading gives the expected vasodilation. Without a change in formulation, Applicant would not recommend the I.V. use of Toradol to reverse acute and life threatening vasospasm or stroke. Multiple medications over the last several years have now been tried for the vasodilators. Each of these classes and results will be discussed in their specific following paragraphs.
With respect to beta blockers, Inderal (Propranolol), Tenormin (Atenolol), Normodyne (Labetolol), Lopressor (Metoprolol) have all been tried. None of these have been significantly effective at vasodilation. However, when using vasodilators, patients will frequently notice waxing and waning of their effectiveness. This is especially noticeable in patients who are beginning to be tapered off their medications due to good responses, and thus cannot tolerate higher doses of vasodilators without developing symptomatic lethargy, hypotension, etc. from the medications. In these patients, Beta blockers have been extremely effective in smoothing out the sympathetic nervous system excitability and variability that may be seen. In Applicant's patient population, Inderal (Propranolol) has been most effective. The other medications have not been effective, although probably are useful in blunting any acute response to Nitroglycerin administration from a hypersensitive Nitric Oxide response, if the patient is prone to such a response. Alpha blockers have been tried. Clonidine has been extremely effective. Hytrin (Terazosin), Ismelin (Guanethidine), Minipress (Prazosin), have been all tried, with less successful

results. Cardura (Doxazosin) is still being tried, but initial results are just now coming available. Dibenzyline (Phenoxybenzamine) has also been tried, and appears to be relatively mild, similar in action on the vasospasm as Hytrin (Terazosin).
Angiotensin Converting Enzyme Inhibitors (ACE) inhibitors have been tried including Accupril (Quinapril), Altace (Ramipril), Capoten(Captopril), Lotensin (Benazepril), Monopril (Fosinopril), Prinivil (Lisinopril), Zestril (Lisinopril timed released), Univasc (Moexipril), Vasotec (Elalapril), Cozaar (Losartan). Accupril (Quinapril) has consistently been the most effective.
With use of Accupril (Quinapril) and concomitant administration of low dose Nitroglycerin, 1/10th inch once a day to several times a day, most patients may be eventually weaned from the use of oral medications, althoughApplicantdo tend to maintain them on low dose Nitroglycerin in perpetuity, as the inciting cause of the vasospasm usually remains and usually causes redevelopment of symptoms.
However, these symptoms and radiological as well as symptomatic vasospasm may be controlled with low dose medication if Accupril (Quinapril) is used initially. The timed release medications such as Zestril (Lisinopril) are extremely effective in part due to increased patient compliance. Although Applicant personally finds these two aforementioned medications the most helpful, Capoten (Captoptil), Lotensin (Benzepril), Prinivil (Lisinopril) are close second tier medications. The other ACE inhibitors tend to be effective, but a third tier alternative drug. However, as a patient becomes intolerant to the stronger ACE inhibitors, these second and third tier drugs may be very helpful in preventing and controlling the vasospasm without developing intolerance to the medication. Similarly, in less severe cases, these are excellent first line drugs.
Calcium channel blockers have been tried. In the most severe cases, Dynacirc (Isradapine) has been extremely effective. Adult (Nifedipine) in standard doses and timed release dosages has been helpful but as a second line drug. Careen (Nicardipine), Nimotop (Nimodopine), Cardizem (Diltiazem), Norvasc (Amlodipine) have been less effective in relieving the vasospasm or in allowing a degree of vascular relaxation sufficient to allow the patient to taper from the medication over time. Sular (Nisoldipine) and Plendil (Felodipine) appears to be slightly milder than Dynacirc (Isradapine) and has been effective in those that could not tolerate Dynacirc. Verapamil in its many manifestations is only rarely used, due to its minimal direct effect on vasodilating the vasculature as documented by Transcranial Doppler or in its ability to affect the outcome of these disorders. Vascor (Bepridil) is just now being tried on some patients. Of course, the general comments concerning ACE inhibitors also apply to these medicines.
Applicant's first line medications may be too strong for the other physicians' patient populations if those practices don't tend to attract as severely impaired individuals. Thus, the second and third tier medications may be better tolerated in less severely affected people, and similarly, as patients are able to taper from medications, they may taper into more mild medications from the same classes as previously were shown to be successful.
Other Vasodilators that have not been previously discussed have also been tried. Hydralazine is effective, but tends to cause significant blood pressure changes in these patients.
Interestingly though, Hydralazine tends to improve the morphology of the diastolic flow component dramatically, which, in view of Hydralazine's effect on arterioles, bolsters the perspective that the diastolic phase of the Transcranial Doppler is a good indicator of downstream runoff. Flolan (Epoprostenol) has not yet been tried, nor has IV Papaverine or Inocor (Amrinone). Reserpine has been extensively used. It can be very effective. It's initial effect is parasympathomimetic. A later effect is sympatholytic. Its role is that it may be very effectively used as an adjunctive drug especially when patients have

difficulty tolerating stronger vasodilators. The dose which initially is most effective of Reserpine frequently needs to be decreased dramatically (generally 50%) approximately 6 weeks into therapy as the sympatholytic activities start to become significant. Antipsychotic agents have also been used. Several of Applicant's patients who Applicant will be reporting on later, were psychotic, and responded well to these medications and had significant vasospasm identified on ultrasound which improved after the administration of medication. Of the antipsychotic, Mellaril (Thioridizine) has not been effective. Thorazine Chlorpromazine) has been moderately effective. Navane (Thiothixene) has been extremely effective, and Respiradol (Respiradone) has generally improved the patient's symptoms, but had no significant improvement on ultrasound. It has been less well-tolerated in comparison with Thorazine and Navane. interestingly enough, most of the patients who were placed on Navane, did not continue to require Navane two to three months after starting the medication, and were able to be weaned from that and had better response to their other vasodilators. In general, Navane was used as a first line drug in patients who had severe elevations of Transcranial Doppler Artery mean flow velocities greater than 1.3, and we would generally expect 50% improvement in the Transcranial Doppler Artery Ultrasound within a half hour of administering Navane by liquid solution. The solution was made by stirring 2 mg of Navane in 4 ounces of water then administered orally. The patients were usually afterwards placed on vasodilators such as ace inhibitors and calcium channel blockers.

PROBLEMS

The approach used in Applicant's clinical practice of over 2,000 patients, is the approach of using vasodilators to treat migraine headache, to cause improvement in closed head injury symptoms, and to treat vasospasm from any cause. This has also been effective in Attention Deficit Disorder (ADD) and multiple other disorders with cerebral ischemia or vasospasm as a component. A partial list of these disorders include Vascular Seizures, Vertigo, Tinnitis, Post Subarachnoid Hemmorhage Vasospasm secondary to both aneurysm rupture or trauma, Stroke, reversal of a chronic stroke penumbra, autism, depression, Post-Traumatic Stress Syndrome, autism, dyslexia, visual disturbances and blindness, Autism, Tourette's Syndrome, Tics, Tremors, Ataxia and multiple other neurocognitive, neuropsychiatric, and neurological disorders that have vasospasm and ischemia as a common aetiology, systemic disorders with diffuse vascular involvement, i.e. some types of Fibromyalgia and Prinz Metal Angina may also be treated with this approach. The approach to treatment and results are essentially identical in these cases, with minor variations.

However, 10% of patients placed on antihypertensives will develop peripheral hypotension before the vasospasm is successfully treated. In those patients, Navane (Thiothixene) and other antipsychotics of that group, have been found to be an extremely effective central vasodilator without causing peripheral blood pressure changes. These patients may do well on low dose Angiotensin Converting Enzyme Inhibitors, Calcium Channel Blockers, Alpha blockers and/or Nitrates with the use of Navane (Thiothixene) and the other anti=A9psychotics of that group and have excellent resolution of vasospasm.

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EXAMPLE - WHIP-LASH/BREAST IMPLANTS/MIGRAINE

Applicant has a baseline practice consisting of mainly post-traumatic, closed-head injuries and post-traumatic migraine disorders of which many have attention deficit disorders,

(ADD). However, several years ago Applicant had a large number of patients who presented with ADD of which the origin of their problems was associated with silicon breast implants (silicon toxicity). What became evident in evaluating of these patients was that the neuropsychological tests, computerized EEG and Transcranial Artery Doppler results were essentially identical. Another common characteristic in these patients was the waxing and waning nature of at least some of their complaints. Those patients with Attention Deficit Disorder both post-traumatic and in particularly those patients with silicon breast implant disease with MS-like syndrome would have normal neurological examination one day and on another day the exam would be normal. This finding substantiated the patients' complaints of waxing and waning of symptoms and seemed to be related to the degree of physiological or psychological stress the patient experienced when being interviewed or tested.

The degree of abnormality of neurological exams would extend to the point of normal or abnormal Romberg and Tandem Gaits, reflex examinations and Babinski examinations in the same patient. Evoked potential test results varied from normal to abnormal on different days and the testing was performed by the same examiners.
In this same time frame, a series of new medications were developed to treat migraine headaches. As headache was a major complaint of many of these patients, Applicant tried these medications out including Imitrex (Sumatriptan), IM Toradol (Ketoralac) and other medications under direct monitoring. As these patients tend to be intractable, it was not expected that any of these medications would have dramatic results. Rather, it was expected that one or another set of medications might help point the way into using specific classes of medications or approaches. Accordingly, each of these patients, equivalent of a large number of patients, is monitored continuously across the day. The patients are hooked up with EEG's or Brain Stem Auditory Evoked Responses, or VEP's, or Transcranial Dopplers, and across the day would have many of the different short-acting medications tried on them to see which would work and which monitoring tool would be most effective in identifying the improvement.

With respect to the different monitoring tools, some were more helpful than others. It was found that the EEG was not very sensitive. The Brain Stem Auditory Evoked Response and other evoked potential tests were very insensitive tools for monitoring, because of the length of time required to perform the test after short-acting medications were given in IM or sublingual or nasal spray administration route. The Transcranial Doppler consistently appeared to give the best indication as to which medications would work. If an ultrasound showed improvement, the patient invariably also reported improvement in their clinical symptoms. These symptoms included not only headache, but also sensations of confusion, balance disorder, abnormal Romberg or Tandem Gait or other neurological abnormalities. If the medications showed evidence of increasing vasoconstriction on the doppler, the patients who had a headache, frequently reported improvement in the headache, but a worsening of their confusional state or a worsening of other neurological symptoms. Those patients were identified as having improvement on ultrasound with doppler also showed resolution of their headache, but did not show the deterioration in other neurological effects.

This was completely unexpected. The general approach towards migraine and headache has always been that the headache represents a vasodilation and frequently a hyperperfusion state. The aura, of course, represents a vasoconstrictive phase. What our results seemed to suggest was that the doppler, which looks at essentially the area of

blood vessels around the base of the brain, was showing vasoconstriction. Vasoconstrictive medicines would relieve the headache presumably through a similar mechanism, as a vasoconstrictive medication probably relieved coronary artery disease. It would relieve it by decreasing the vasodilation that occurs downstream from the area we are able to directly insonate. Unfortunately, if cerebral artery disease is anything like coronary artery disease, that downstream dilation represents an attempt by the body to compensate and maintain perfusion to thus becoming ischemic.

In Applicant's patient population, all medications which resulted in vasoconstriction, relieved the headache, but caused neurological deterioration. As the medication wore off, as documented by the patient's clinical symptoms, sonography data, the patient's neurological abnormalities improved. Similarly, those medicines which resulted in direct vasodilation such as Hydralazine (Apresoline), Nitroglycerin and other medications all resulted in improvement in the patient's headache, but also resulted in improvement of any other neurological abnormalities including balance disorders, gait disorders, hemiparesis, abnormal Babinski's and abnormal reflexes.

OBSERVATIONS NOTED CONCERNING TRANSCRANIAL DOPPLERS

A special word about Transcranial Doppler needs to be made. We found that morphology of a Transcranial Doppler Artery Ultrasound is as important as mean flow velocities. In our patients, as they became more normal, and as their fixed deficits and neuropsychological abnormalities resolved etc., the morphology of the wave form would be similar to that of an internal carotid artery tracing. We did not find that there would be elevation of flow readings throughout diastole, as is more commonly published. It is important to identify that the original normative data obtained in 1979, used for "Normals" patients with post-traumatic migraine disorders, "psychogenic seizures", and the interictal migraine phase may not be appropriate. It is important to note that other labs which have done less extensive studies of normal versus non-normal, may have unknowingly used many patients with a history of migraines or whiplash headaches.

Some have not identified the close relationship between degree of vasospasm and clinical abnormalities. This may be due to less lengthy monitoring or evaluations being carried out by those labs in comparison to our own. Equally, the trend clinical correlation is a general one. Remembering hemodynamics, it is important to note that if the blood vessel is constricted, patients do have a limited ability to compensate for the effects of that vasoconstriction by dilating distally to the constricted area. Patients will not be abnormal clinically during the early stages of constriction of an artery. It is only once the downstream area is no longer able to dilate to a degree enough to maintain a significant pressure gradient across the vasoconstricted area that the patient will develop symptoms. It is important to continue to monitor and treat these patients until the sonographic studies return to normal and beyond. Realizing that blood vessels constrict across the day in response to sympathetic nervous system variability, internal steroid release, physiological and psychological stress, including the physiological stress of photic stimulation, driving etc., and thus to obtain an ultrasound at one moment, must be correlated with the patient's clinical symptoms and any complaints of variability across the day.

We also found that over time, chronic, untreated patient studies frequently falsely appear to normalize with a dropping of mean flow velocities. This occurs as the body develops compensating mechanisms to relieve the ischemia. Thus morphology becomes extremely

important in identifying those who have ongoing vasoconstrictive disorder intracranially. The development of a pattern as time goes on is to have a blunted upstroke in the systolic portion of the ultrasound, but with an overall mean flow velocity of less than .6 meters per second. That blunting, which is also seen in disseminated vascular disease from any cause, is highly suspicious for severe vasospastic disorder. A computerized EEG or standard EEG consistent with brain dysfunction or ischemia, and/or neuropsych testing consistent with variability of cognitive injury (especially with fluctuating cognitive deficits across several hours or days of testing) with ischemia is often helpful as a corroborating study. These are patients who should not be treated initially with Nitroglycerin or other potent medications, but should first have other medications which are direct vasodilators instituted at low doses and slowly advanced as the patient is able to tolerate it. This institution with alternative vasodilators, tends to decrease the incidence of a potentially dangerous nitric oxide sensitivity reaction.

With respect to Nitroglycerin, what we have seen is several time courses of the effect of Nitroglycerin. The first is an acute effect which lasts between 15 and 45 minutes. The method of administration being a patch, pill or sublingual spray determines the rapidity of absorption and distribution. It seems to have a lingering effect for approximately 2 to 3 hours. Nitroglycerin then gets converted into a variety of subsidiary byproducts, all with some vasodilating properties. Each of these medications themselves can accumulate in patients to toxic doses, and can cause a reactive cerebral vasoconstriction. Thus, it is easier to maintain patients on intermittent low dose Nitroglycerin applications, then chronic applications of medication, as the clinical data and clinical response to the vasodilator challenge becomes confused. With respect to Nitric Oxide sensitivity, those patients in Applicant's clinical practice who have not been premedicated with a beta blocker, an alpha blocker or a direct vasodilator such as a calcium channel blocker or an ACE inhibitor, who are given their first dose of Nitric Oxide and developed acute erythema of the nose or face, are having a reactive vasoconstriction and distal vasodilation occurring at the same time. Those patients on Transcranial Doppler Artery Ultrasound will have acute spasm of the arteries and active constrictions and dilations may frequently be seen. Those patients may have a seizure or a stroke or a blackout spell. This problem can be immediately reversed with IM Toradol(ketoralac). Toradol in 90 to 120 mg IM doses causes acute vasodilation on ultrasound in most patients. In lower doses, the Transcranial Doppler Artery Ultrasounds generally do not show significant changes, but the patient reports a symptomatic improvement.

IV Toradol in 30 to 60 mg doses does not cause any improvement on Transcranial Doppler Artery Ultrasound, and patients generally report a sensation of vertebrogenic syndrome with increase in spaciness, confusion, worsening headache and worsening spasm. Although I have not identified this directly, their clinical course is that of a development of a vasoconstricted vertebral or basilar artery syndrome. This probably relates to a carrier drug in the I.V. Toradol solution. Without a change in formulation, Applicant would not recommend the I.V. use of Toradol to reverse acute and life threatening vasospasm or stroke.

Multiple medications over the last several years have now been tried for the vasodilators. A discussion of these will follow. It should be recognized, that Applicant's patients tend to be the most severe cases in our area. Accordingly, for me, the medications that have been most effective have also been among the strongest. The less strong medication will undoubtedly be very helpful in less severe cases. In all cases, as the vasospasm may be

subclinical or affecting portions of their cognitive abilities that they do not routinely use, patients can not be considered as reliable in identifying when the vasospasm is resolved. Accordingly, ongoing monitoring of therapy with functional tests such as EEG or Neuropsych testing and imaging tests like ultrasound are vital for evaluation of response to therapy.

With respect to Beta Blockers, Inderal (Propranolol), Tenormin (Atenolol), Lopressor(Metoprolol Tartrate) and Normodyne (Labetolol) have all been tried. None of these have been significantly effective at vasodilation. However, when using vasodilators, patients will frequently notice waxing and waning of their effectiveness. This is especially noticeable in patients who are beginning to be tapered off their medications due to good responses, and thus cannot tolerate higher doses of medications of vasodilators, but still have residual vasospasm. In these patients, Inderal has been extremely effective in smoothing out the sympathetic nervous system excitability that may be seen. The other medications have not been as effective, although probably are useful in blunting any acute response to Nitroglycerin administration from a hypersensitive Nitric Oxide response, if the patient is prone to such a response.

Alpha blockers have been tried. Hytrin (Terazosin) has not been found to be effective. Catapress (Clonidine) has been extremely effective. Minipress (Prazosin) has been significantly effective and frequently better tolerated in the long run than Clonidine, although in Applicant's patients, it seems to treat the problem successfully enough to prevent the symptoms, but not enough to allow complete resolution of the vasospasm. Cardura (Doxazosin) has been a relatively mild medication. Aldomet (Methyldopa) has been useful in some patients. Reserpine has been an extremely effective medication. In the short term, it is helpful due to the parasympathomimetic effect, which tends to decrease the activity of the Sumpathetic nervous system. Later, its direct sympatholytic action is very effective. Frequently, a dose needs to be adjusted downward approximately 6-10 weeks after institution of therapy. It has even been useful in treating migraine induced depression due to chronic vasospasm with or without headache in those patients who could not tolerate other vasodilators. Clonidine has also been useful in these depressed patients who could not respond to other vasodilating medications.

ACE inhibitors have been tried. With use of ACE inhibitors and concomitant administration of low dose Nitroglycerin, 1/10th inch once a day to several times a day, most patients may be eventually weaned from the use of oral medications, althoughApplicantdo tend to maintain them on low dose Nitroglycerin in perpetuity. Other Angiotensin Converting Enzyme Inhibitors, including Capoten (Captopril), Altace (Ramipril), Lotensin (Benazepril), Monopril (Fosinopril), Prinivil (Lisinopril), Vasotech (Enalapril), and an ACE inhibitor have also been tried. I suspect that ACE inhibitors work the best due to its activity on the Nitric Oxide pathway. It is most effective at reversing the vasospasm when used in conjunction with low dose nitrates.

Calcium channel blockers have been tried. The most effective has been Dynacirc (Isradapine). Much less effective have been, in descending order of effectiveness, Nifedipine, Nimodopine, Plendil (Felodipine), Dilacor (Diltiazem), Cardene (Nicardipine) and, Norvasc (Amlodopine) and finally, Verapamil.

Other agents that deserve special mention include Toradol IM in doses of 90-120mg. In lower doses, this is not so effective. Unfortunately, due to the new FDA guidelines,

Applicantno longer use this medication in these doses. Hydralazine is effective, but tends to cause significant blood pressure changes in these patients. Interestingly though, Hydralazine tends to improve the morphology of the diastolic flow component dramatically which in view of Hydralazine's effect on arterioles. bolsters the perspective that the diastolic phase of the Transcranial Doppler is a good indicator of downstream runoff.

Psychiatric agents frequently have vasoactive effects. Prozac, and other non-vasoconstricting medications are helpful. Those known to cause vasoconstriction tend to aggravate the spasm and neurological abnormalities. Antipsychotic agents have also been used. Several of Applicant's patients who ApplicanT will be reporting on later. were psychotic. and responded well to these medications and had significant vasospasm identified on ultrasound which improved after the administration of medication. Of the antipsychotics, Navanne (Thiothixene) has been the most effective. Thorazine (Chlorpromazine) has been moderately effective. Respiradol has generally improved the patient's symptoms, but had no significant improvement on ultrasound. It has been less well-tolerated in comparison with Thorazine and Navane. Interestingly enough, most of the patients who were placed on Navane, did not continue to require Navane two to three months after starting the medication, and were able to be weaned from that and had better response to their other vasodilators. In general, Navane was used as a first line drug in patients who had severe elevations of Transcranial Doppler Artery mean flow velocities greater than 1.3, and we would generally expect 50% improvement in the Transcranial Doppler Artery Ultrasound within a half hour of administering Navane by liquid solution. The solution was made by stirring 2 mg of Navane in 4 ounces of water then administered orally. The patients were usually afterwards placed on vasodilators such as ACE inhibitors and Calcium channel blockers. Mellaril (Thioridazine) has had no significant effects.

Of the Anti-epileptic drugs, including Dilantin (Phenytoin), Tegretol (Carbamazepine) and Depakote (Valproate), none of the medications in therapeutic doses have changed the vasospasm. but all have improved in some patients the EEG abnormalities and their neurocognitive or neurological complaints.

PROBLEMS

The approach used in Applicant's clinical practice of over 2,000 patients, is the approach of using vasodilators to treat migraine headache, to cause improvement in closed head injury symptoms. and to treat disorders diverse and including seizures, stroke, syncope, attention deficit disorder. vertigo, autism. depression. psychosis. transient global amnesia. Multiple Sclerosis and Multiple Sclerosis like syndrome. but not limited to these disorders.

However, approximately 10% of patients placed on antihypertensives will develop peripheral hypotension before the vasospasm is successfully treated. These patients appear to have an increased peripheral vasodilation to central vasodilation in response to the medication.

In these patients. several approaches may be used. The pharmacological approach is to mix several medications of different classes at submaximal doses to achieve a synergistic response. An alternative approach is to use medications such a Toradol or antipsychotic

medications that also dilate primarily the vascular bed of the Central Nervous System and not that of the peripheral. In those patients, Navane and the antipsychotic of that group, have been found to be an extremely effective central vasodilator without causing peripheral blood pressure changes. Patients placed on these agents are frequently able to tolerate low dose ACE inhibitors. Calcium Channel agents, or other peripheral vasodilators without developing hypotension and still have excellent resolution of vasospasm. The structural approach is to search for an underlying aggravating problem affecting the sympathetic nervous system. This is usually caused by an injured area of the body which may include joint injuries, disk injuries, nerve injuries, etc. One of Applicant's patients developed severe neurocognitive problems and neuropsych abnormalities, EEG problems, and vasospasm, from a Carpal Tunnel Syndrome. The correction of that problem, or any other irritant to the Sympathetic Nervous system by blocking the irritant or removing it, may result in a decrease in the autonomic hyperactivity, and an improved response to medication. A third approach is to sympathetically denervate the vasculature. This may be partially performed with Epidural Steroid Injections with or without anaesthetic, Facet or Perifacet blocks, Rhyzolysis, Stellate Ganglion Blocks, and Neurolyses and similar procedures. In Applicant's practice, procedures oriented towards the innervation of the Carotid arteries tend to cause Anterior and Middle Cerebral artery relaxation. This clinically results in increase concentration/memory and decreased mood/personality problems and language problems and other frontal and temporal lobe disorders. Posterior circulation denervation tends to decrease occipital headaches, and improve balance, vertigo, and visual complaints and have secondary cognitive effects (probably through perforating vessel contributions). Blocks tend to work for a dramatically shorter period of time than do neurolysis procedures.

Chiropractic procedures may be very helpful as may Biofeedback and counselling procedures to decrease the Autonomic hyperactivity. These techniques may also be useful adjuncts to treatment in the chronic patient.

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